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Original Article

Back-to-back colon capsule endoscopy and optical colonoscopy in colorectal cancer screening individuals.

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Abstract:

Aim: To determine the polyp detection rate and per-patient sensitivity for polyps >9 mm of colon capsule endoscopy (CCE) compared with colonoscopy as well as the diagnostic accuracy of CCE.

Method: Individuals who had positive immunochemical faecal occult blood test during screening had investigator blinded colon capsule endoscopy and colonoscopy. Participants underwent repeat endoscopy if significant lesions detected by colon capsule endoscopy were considered to have been missed by colonoscopy.

Results: There were 253 participants. The polyp detection rate was significantly higher in colon capsule endoscopy compared with colonoscopy (P=0.02). The per-patient sensitivity for >9mm polyps for CCE and colonoscopy was 87% (95%CI: 83%-91%) and 88% (95% CI: 84-92) respectively. In participants with complete colon capsule endoscopy and colonoscopy examinations (N=126), per-patient sensitivity of >9 mm polyps in colon capsule endoscopy (97%; 95% CI: 94-100) was superior to colonoscopy (89%; 95% CI: 84-94). A complete capsule endoscopy examination (N=134) could detect patients with intermediate or greater risk (according to the European guidelines) with an accuracy, sensitivity, specificity and positivity rate of 79%, 93%, 69% and 58% respectively, using a cut-off of at least one polyp >10 mm or more than two polyps.

Conclusion: Colon capsule endoscopy is superior to colonoscopy in polyp detection rate and per-patient sensitivity to >9 mm polyps, but only in complete CCE examinations. The rate of incomplete colon capsule endoscopy examinations must be improved.

Keywords: Colon capsule endoscopy, Colonoscopy, Colorectal cancer screening

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What does this paper add to the literature?:

With a complete examination, CCE is a highly sensitive method of detecting neoplasia in the colon and is more sensitive than colonoscopy. We believe that, with increasing completion rates, appropriate rapid reporting and refined bowel preparation, CCE could have a significant impact on CRC screening.

Introduction:

Colorectal cancer (CRC) screening has been implemented in many European countries in order to detect early cancers and high-risk adenomas with the primary aim of reducing colorectal cancer mortality. Most screening programmes include a two-stage procedure with a primary faecal occult blood test (FOBT) followed by optical colonoscopy (OC) for positive tests. The efficacy of the screening is hampered by the suboptimal sensitivity and specificity of FOBT [1] and imperfect OC[2] sensitivity and low population acceptance rates. This necessitates repeated screening rounds and results in missed lesions, interval cancers, unnecessary investigations and a substantial burden on endoscopy and pathology units. The development of alternative strategies is desirable to reduce the number of colonoscopies without compromising the effect of screening.

Colon capsule endoscopy (CCE) is a relatively new technique that has been proposed as a filter for referral to OC in CRC screening programmes, and was found to reduce the need for colonoscopy by 71% in a study of 63 individuals[3]. The second generation CCE has a reported sensitivity and specificity for detecting polyps of >9 mm of 87% and 95%, respectively.[4]. Two studies, of 50 and 62 patients, have investigated the accuracy of CCE compared with colonoscopy in immunochemical fecal occult blood

test(IFOBT) positive screening individuals, reporting sensitivities and specificities for polyps >9 mm from 89-93% and 92-96%, respectively [3, 5]. The present study is currently the largest trial investigating the polyp detection rate (PDR) and accuracy of second-generation CCE compared with OC in an immunochemical FOBT (IFOBT) positive screening population.

The primary aim of this study was the PDR of CCE compared with OC. Secondary outcomes were the sensitivity of CCE to detect patients with >9 mm polyps compared with OC, and the ability of CCE to detect individuals at intermediate risk or greater according to the European guidelines for stratification of colorectal cancer screening risk [6].

Method:

This was a prospective comparative study of IFOBT positive screening individuals investigated with second generation CCE, compared with a screening colonoscopy performed the next day. When significant findings on CCE were suspected to have been missed by OC, participants were offered a repeat endoscopy. Trial participants were recruited from the first round of the national CRC screening programme on the island of Funen, Denmark. In Denmark, all citizens aged 50-74 years are invited to have a single sample IFOBT (OC-Sensor DIANA; Eiken Chemical Co., Japan) with a hemoglobin concentration cut-off level of 20µg haemoglobin per gram of faeces (Hb/gF). Invitations to participate in the study were distributed alongside the letter informing the person that the IFOBT test was positive and the consequent invitation for OC. Exclusion criteria were previous bowel surgery (except appendicectomy), inflammatory bowel disease, renal insufficiency, cardiac pacemaker and symptoms of bowel obstruction. Participants were scheduled for CCE one day prior to the planned OC. The CCE examination was performed using PillCam Colon II (Medtronic, USA) as a home delivered service by trained nurses (Corporate Health, Germany), who supported the participants throughout the procedure. Bowel preparation was polyethylene glycol based solution (Moviprep, Norgine, Denmark) for cleansing and boosters (Table 1). All OC's were performed at a

single centre by trained senior endoscopists who had been approved for screening investigations using Evis Exera III 190 colonoscopes and scope guides (Olympus, Japan). The endoscopists were blinded to the results of the CCE examination. They reported bowel preparation quality and all neoplastic findings by anatomic location, morphology and size. Pathology reports were conducted according to the European guidelines for colorectal cancer screening[6]. The CCE report was provided in three working days by trained staff (Corporate Health, Hamburg, Germany) using Rapid Reader Software (Medtronic, USA). It included information on capsule excretion (complete transit whilst recording), transit time, bowel preparation quality, and anatomic location of findings, morphology, and size. For the anatomic location of lesions, the colon was divided into three sections (right, transverse and left colon including rectum). Bowel preparation was evaluated in OC and CCE on a five point scale (not acceptable, poor, intermediate, good and excellent). Preparations rated as excellent, good, intermediate or poor were defined as clinically acceptable in CCE and OC. The CCE and OC reports were evaluated by one of two senior consultants and the participants were informed of the results. If OC was incomplete due to insufficient preparation or inability to reach the caecum patients underwent either repeat colonoscopy or CT colonography. If significant lesions were found at CT colonography, patients had another colonoscopy under general anaesthesia. Findings from these examinations were included in the OC findings. In the case of suspected missed polyps by OC the participants were offered a repeat endoscopy and in all cases where a second endoscopy was performed the endoscopist was unblinded to the findings of the CCE examination. After completion of all endoscopic examinations, participants were risk stratified according to the European guidelines for colorectal cancer screening [6].

Statistical methods

Sample size was calculated as non-inferiority between CCE and OC estimating a PDR in CCE and OC of 70%, a power of 80%, alpha of 5% and delta of 10%, rendering a total of 260 individuals acting as their own control. All polyps found during any OC, including the repeat endoscopies occasioned by the CCE findings or subsequent therapeutic endoscopies for polyp removal, were considered true positive findings. Thus,

findings made by CCE and OC were compared with all findings after completion of additional endoscopies when calculating accuracy of CCE and OC in polyp detection. Polyps reported at CCE were matched to polyps found in OC by size only, using a per-patient approach. If a size of +/- 50% of the CCE measure overlapped with a size of +/- 50% by endoscopist or pathologist measure, it was considered a potential match. Polyps could be size matched regardless of location. Based on the size of the largest polyp found, patients were categorized as having >9 mm polyps or not. The largest measured size by CCE, endoscopist or pathologist was used. Analyses of PDR and per-patient sensitivity and specificity were done for all participants and for the subgroup of participants who had a complete CCE and a complete OC. Analyses of CCE accuracy in risk stratification was performed on all participants with a complete CCE. Statistical analyses were conducted using STATA 14 (Texas, USA). Results are expressed as proportions or rates with 95% confidence interval (95%CI) and compared using the chi-squared test as appropriate. A *p*-value <0.05 was considered significant.

Ethics

All included participants received oral and written information and gave signed informed consent. The trial was registered at clinicaltrials.gov (NCT02303756) and approved by the local ethics committee (S20140141), and the Danish data protection agency.

Results:

A total of 1458 consecutive invitations were sent out to IFOBT positive individuals and 380 called the project nurse for consideration of inclusion. Seventy-four were excluded and 306 individuals initially consented to participate, but 45 withdrew their consent before the examinations were scheduled. Seven individuals were excluded before the examinations as they did not adhere to the bowel preparation

protocol (n=6) or were not able to swallow the video capsule (n=1). One individual was excluded because consent was withdrawn subsequent to the CCE examination. A total of 253 participants underwent CCE and OC and provided data for analyses (figure 1). Fifty-eight percent were men, and the median age was 64 years.

CCE and OC completion rates

The completion rate of OC examinations (90%; 95% CI: 86-94) was significantly higher (p<0.001) compared with CCE (54%; 95% CI: 48-60). A total of 126 participants (50%) had a complete CCE and OC and were included in the subgroup analyses of per-patient sensitivity and specificity. The estimation of bowel preparation was significantly better (p<0.001) in OC (95% acceptable; 95% CI: 92-98) compared with CCE (85% acceptable; 95% CI: 81-89). The rate of capsules excreted while recording (CCE excretion rate) was 57%, but eight of the 145 excreted had an unacceptable bowel preparation, leaving 137 (54%) suitable for a complete diagnostic investigation, and were included in CCE risk stratification accuracy analyses. For excreted capsules the transit time was <10 hours for 90% (95% CI: 85-95), and the recording time in the incomplete examinations exceeded 12 hours in 83% (95% CI: 76-90).

Adverse events

There were no serious adverse events related to the diagnostic procedures of CCE and OC. There were no retained or impacted capsules, and no bowel preparation or booster related complications or side effects. However, of the 26 therapeutic endoscopies performed with endoscopic mucosal resection there were seven complications. Five had rectal bleeding, of whom one required blood transfusion and three underwent endoscopy to ensure haemostatic control. Two participants had bowel perforation, one was managed conservatively and one had surgery.

CCE and OC findings

There was a significantly higher PDR in CCE compared with OC in all patients (74% and 64% respectively, p=0.02), and in CCE compared with OC in those undergoing complete investigations (86% and

65% respectively, *p*<0.001) as shown in Table 2. Adenoma detection rate (ADR) in OC was 53% (95%CI: 47-59).

The total number, size, location and pathology of polyps found by CCE, OC, and repeat endoscopies are shown in Table 3. CCE and OC detected a total of 483 and 434 polyps respectively. Polyps were reported as larger by CCE compared with OC and CCE reported a higher proportion of polyps in the right colon, while OC reported a higher proportion in the transverse colon. In the left colon findings were comparable. Sixty percent of all polyps retrieved by OC were adenomas. 13% of polyps removed were lost and not retrieved for pathology. Eleven adenocarcinomas were confirmed by OC and histology. In five of these the CCE reported suspicious large mass at the correct location and in two patients CCE reported a matching polyp that was later found to harbour cancer. In four participants, due to incomplete transit, the capsule did not pass the site of cancer while recording.

Repeat endoscopic findings:

Fifty-three individuals (21%) underwent repeat endoscopy due to findings on CCE, considered to be missed at OC (table 3). As a result, 82 additional polyps were retrieved, contributing to 16% of all polyps detected. Twenty-four of these polyps were >9 mm and 11 participants with no detected >9 mm polyps on OC had a >9 mm polyp retrieved at repeat endoscopy. Forty-six percent of polyps were found in the right colon and 46% of the polyps were adenomas. PDR and ADR at the repeat endoscopies were 85% and 59% respectively. The adenomas retrieved at the repeat endoscopies increased the ADR in all participants from 53% to 57% (*P*=0.37), and resulted in risk reclassification of 12 individuals with an additional 5 high risk, 3 intermediate risk and 4 low risk patients who had no findings at OC.

Sensitivity and specificity:

The CCE per-patient sensitivity and specificity (Table 4) for polyps >9 mm for all participants were 87% (95%CI: 83%-91%) and 92% (95%CI, 89%-95%) respectively compared with 88% (95% CI: 84-92) and 100% (95% CI: 100) in OC. In the complete investigations group, the CCE per-patient sensitivity and specificity was

97% (95%CI: 94-100) and 90% (95%CI, 85%-95%) respectively compared with 89% (95% CI: 84-94) and 100% (95% CI: 100) for OC. Comparing only complete examinations, CCE sensitivity was higher than OC, while OC had a higher specificity.

Risk stratification accuracy of CCE:

Figure 2 demonstrates the CCE accuracy, sensitivity and specificity in detecting individuals at intermediate risk or greater and the CCE positivity rate according to a continuum of polyp size thresholds determined by the size of the largest reported polyp in complete CCE examinations (N=137). The maximal accuracy of 85% was reached with a threshold polyp size of 11 mm, with a sensitivity of 88%, a specificity of 82% and a positivity rate of 48%.

Figure 3 demonstrates the CCE accuracy, sensitivity and specificity in detecting individuals at intermediate risk or greater and the CCE positivity rate according to a continuum of polyp number thresholds determined by the reported number of polyps in complete CCE examinations (N=137). The maximal accuracy of 72% was reached with a threshold polyp number of more than two, with a sensitivity of 58%, a specificity of 83% and a positivity rate of 34%.

When the two criteria were combined (at least one polyp ≥ 11 mm or ≥ 3 polyps detected) the accuracy of CCE was 79%, with a sensitivity and specificity of 93% and 69% respectively and a positivity rate of 58%.

Discussion:

This is the largest trial performed to date investigating the performance of CCE against OC in a screening programme of IFOBT positive individuals. It is also the first trial to consistently report PDR for CCE and OC as well as ADR for OC as an OC quality measure. This outcome has been shown to correlate with the risk of interval cancer [7] and is widely used as a screening quality indicator. Despite a poor CCE completion rate in this trial, PDR was significantly higher in CCE compared with OC overall. CCE was also superior in per-patient sensitivity of polyps >9 mm in complete examinations. Unsurprisingly OC had a perfect sensitivity

since the method is not prone to false positive findings. In OC the completion rate, ADR, and proportion of polyps lost were similar to or better than the national average according to the national CRC screening database in Denmark (90% vs. 87%, 53% vs. 50 % and 13% vs. 26% respectively)[8]. This confirms that the quality of the colonoscopies performed was good, providing a sound basis for comparison. The low excretion rate of CCE in this study is insufficient for routine clinical use and impacts the overall performance of CCE, resulting in four adenocarcinomas not observed by CCE due to incomplete examinations. All four undetected cancers were situated distally in the colorectum and in a position not investigated by the capsule. This suggests that an incomplete CCE examination in an IFOBT positive screening individual would have to be supplemented by optical endoscopy. The poor excretion rate is likely to have been due to the lack of a potent booster, but the design of this study was constrained by the regulations of the national screening programme which stipulates that only Moviprep® may be used as a booster for safety reasons. Our study strongly indicates that better booster regimens should be used to make CCE feasible in CRC screening; excretion rates of >90% have been reported in several trials using more powerful boosters [9-11] demonstrating that high excretion rates are feasible and that attention to the choice of bowel preparation and boosters in future trials is important.

The discrepancy between polyps reported by CCE and OC can be caused by either false positive findings by CCE or false negative findings by OC. We believe, the discrepancies are mostly due to false negative findings in OC, because a substantial number of additional polyps were found by repeat endoscopy and an appreciable miss-rate by OC has been well established by back-to-back colonoscopy [2]. The delay between CCE and OC could have resulted in a poorer preparation at OC compared with daily clinical practice, resulting in polyps being missed. CCE reported polyps as being larger than OC, but pathology measures were also larger than OC measures, suggesting that there might be underestimation of polyp size by OC and overestimation by CCE. There were also differences in the proportion of polyps reported according to the different colonic segments examined between OC and CCE, but due to the high rate of incomplete CCE examinations, numbers are difficult to compare.

The IFOBT sensitivity for small adenomas has been reported to be 7%[12]resulting in the vast majority of potentially low risk individuals being IFOBT negative. This indicates that the primary screening health benefit arises from advanced adenoma and cancer detections. The high sensitivity of complete CCE examinations in detecting individuals later classified as intermediate risk or greater, is thus an acceptable basis for being a filter test in CRC screening. The individuals at risk missed by this approach are likely to be outweighed by more effective colonoscopies after CCE because the endoscopists could be guided by the CCE findings.

With the level of complete CCE examinations reported in this paper, CCE is clearly not yet suitable for introduction into the screening algorithm. However, we have shown that, in a substantial proportion of patients, it is feasible to carry out OC as a next-day procedure after CCE using the same bowel preparation and that, with complete examination, CCE is a highly accurate method of detecting neoplasia in the colon. Indeed, we have shown that for neoplasia, a complete CCE is likely to be more sensitive than OC. We therefore believe that, with appropriate rapid reporting and refined bowel preparation techniques CCE could have a significant impact on CRC screening. Future research should focus on these areas, on classification and recognition of significant disease and on the cost effectiveness of screening strategies incorporating CCE.

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Table 1: Bowel preparation and booster regimen

Day	Preparation
-2	Morning: 1000 mg oral magnesium-oxide 2 L of water Evening: 1000 mg oral magnesium-oxide
-1	Clear fluids diet Evening: 1 L Moviprep and 2½ L of water
0	Morning: 1 L Moviprep and 1½ L of water. 60-90 minutes of fasting **Capsule ingestion** with 20 mg oral domperidon Booster 1: ¾ L Moviprep and ½ L Water Booster 2: ¼ L Moviprep and ¼ L of water 10 mg rectal bisacodyl Clear fluids diet
1	**Colonoscopy**

Table 2: Polyp detection rate (PDR) by colon capsule endoscopy (CCE) and optical screening colonoscopy (OC) and adenoma detection rate (ADR) by OC.

	All participants (N=253)			**Complete investigations group (N=126)**		
	OC	CCE	P-value	OC	CCE	P-value
PDR, % (95% CI)	64 (58-70)	74 (69-79)	0.02	65 (57-73)	86 (80-92)	<0.001
ADR, % (95% CI)	53 (47-59)	N/A		52 (43-61)	N/A	

Table 3: Polyps detected in Colon capsule endoscopy (CCE), optical colonoscopy (OC) and repeat endoscopy by size, location and pathology.

	CCE (N=253)	OC (N=253)	Repeat endoscopy (N = 53)
Total polyps detected, N	483	434	82
Size, N (%)			
< 6 mm	141 (29)	216 (50)	36 (44)
6-9 mm	183 (38)	115 (26)	18 (22)
> 9 mm	159 (33)	93 (21)	24 (30)
Unknown	0 (0)	10 (2)	4 (5)
Location, N (%)			
Right colon	168 (35)	98 (23)	38 (46)
Transverse colon	32 (7)	51 (12)	13 (16)
Left colon/Rectum	281 (58)	285 (66)	30 (37)
Unknown	2 (0)	0 (0)	1 (1)
Pathology, N (%)			
Non-neoplastic		107 (25)	30 (37)
Adenoma, LGD‡		255 (59)	38 (46)
Adenoma, HGD§	N/A	4 (1)	0 (0)
Adenocarcinoma		11 (3)	0 (0)
Unknown		57 (13)	14 (17)

‡LGD: Low grade dysplasia,§High grade dysplasia.

Table 4: Per-patient sensitivity and specificity in detection of polyps by colon capsule endoscopy (CCE) and optical screening colonoscopy (OC), compared with all findings by all OC's including repeat endoscopies.

	All participants (N=253)		Complete investigations group (N=126)	
	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
CCE				
polyps >9 mm	87 (83-91)	92 (89-95)	97 (94-100)	90 (85-95)
OC				
polyps >9 mm	88 (84-92)	100 (100)	89 (84-94)	100 (100)

*CCE: Colon capsule endoscopy, ^OC#: Sequentially numbered optical screening colonoscopy, ~CT: Computed Tomography

Figure 1: Flowchart

Figure 2

Figure 3